DYSLIPIDEMIA

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Lipids

- Essential substrates for cell membrane formation and hormone synthesis, provide free fatty acids
- Lipoproteins (LP)
  - Serum transport vehicles for cholesterol, triglycerides and phospholipids
  - LDL, HDL, VLDL
  - VLDL is LDL precursor, mostly carries TG
- TC is cholesterol being carried by all LPs
- HDL transports cholesterol from arterial walls or extrahepatic tissue to liver for processing
- LDL transports cholesterol to extrahepatic tissue and can enter arterial walls

Hyperlipidemia

- Defined as elevation in TC, LDL, TG, or low HDL
- Primary HLD is caused by a variety of genetic mutations in LP synthesis and metabolism, coupled with environmental factors
- Longitudinal studies show risk for CVD directly proportional to TC and LDL levels
- LDL = TC – (HDL + TG/5)
  - If TG > 400 mg/dL, LDL must be measured directly

Hyperlipidemia

- Various secondary factors exist:
  - Non-pharmacological: hypothyroidism, liver disease, DM, obesity, malnutrition, malabsorption, AIDS, sepsis, pregnancy..
  - Pharmacological: estrogens, progestins, anabolic steroids, thiazides, glucocorticoids, βBs, protease inhibitors, cyclosporine, isotretinoin..
- 'Normal' values
  - HDL ≥ 40
  - TG < 150
  - TC < 200 mg/dL

Atherosclerosis

1. LP migration into endothelial wall forms a *fatty streak*
2. Oxidation of LP in fatty streak causes endothelial injury and triggers low-grade inflammatory response
3. Macrophage recruitment allows enhanced uptake of lipoproteins and formation of lipid-rich *foam cells*
4. Accumulation of foam cells forms lipid-rich core of atherosclerotic plaque which gets covered by a protective fibrous cap
5. Fibrous cap rupture initiates thrombosis and ACS

Signs/Symptoms/Labs

- Symptoms
  - Generally asymptomatic until complications occur
- Signs
  - Pancreatitis, eruptive xanthomas, obesity/central obesity
- Labs
  - Fasting lipid profile (TC, LDL, HDL, TG)
  - Any other labs or tests related to secondary causes or to complications (lipase/amylase, angiogram, stress test, thyroid function test, HIV, etc.)
  - Adults > 20 should be screened at least every 5 yrs

ATPIII Guidelines

- Based on estimation of 10-yr CHD risk and using it to set LDL goal for therapy
- Framingham score uses age, TC, smoking, HDL, SBP to calculate 10-yr CHD risk
- LDL goal ranged from < 70 to < 160 mg/dL depending on 10 yr risk for CHD
- Statins were first line therapies but combining therapies was allowed to achieve goals

ATP III Vs. 2013 ACC/AHA guidelines

- Based on the conclusion that ASCVD events are reduced by using the max tolerated statin dose in those groups shown to benefit, and that not enough evidence exists for use of non-statin drugs for ASCVD prevention
- Treating to set targets
  - Not supported by clinical trials
  - May result in under-treatment with statins
  - May result in overtreatment with non-statins
  - Does not take into consideration AEs from using multiple agents to attain target

2013 ACC/AHA guidelines

- Statin benefit groups for ASCVD reduction:
  1. Those with clinical ASCVD (CAD, stroke/TIA, PAD)
  2. Individuals with LDL ≥ 190 mg/dL
  3. Individuals 40-75 years of age with DM and with LDL of 70-189 mg/dL and without ASCVD
  4. Individuals w/o clinical ASCVD or DM who are 40-75 years of age and with LDL of 70-189 but with estimated 10-yr ASCVD risk ≥ 7.5%

2013 ACC/AHA guidelines
Secondary Prevention of ASCVD

1. High intensity statin therapy should be initiated or continued as 1st line therapy in men or women ≤ 75 years of age who have clinical ASCVD (ACS, hx MI, stable/unstable angina, stroke, TIA, PAD)
2. Moderate-intensity statin therapy can be used as 2nd line if high-intensity not tolerated

2013 ACC/AHA guidelines
Primary Prevention of ASCVD

- Pts with with primary HLD of LDL ≥ 190 mg/dL should be treated with high-intensity statin therapy as 1st line, or maximum tolerated statin intensity as 2nd line
- In pts with DM and LDL 70-189 mg/dL, moderate-intensity statin therapy is recommended, with optional high-intensity statin therapy if 10-yr ASCVD risk ≥ 7.5%
- Use of statin therapy is optional and based on risk:benefit and pt preference in those with DM who are < 40 or > 75 years of age

2013 ACC/AHA guidelines
Primary Prevention of ASCVD

- In pts without DM and with LDL 70-189 mg/dL who are between 40-75 years of age, 10-yr ASCVD risk should be used to evaluate benefit from prevention with statins
  - ≥ 7.5% → moderate- to high-intensity statin therapy should be given
  - 5% to 7.5% → reasonable to offer moderate-intensity statin therapy
- No recommendation can be made in pts with NYHA class II-IV or on hemodialysis. Decision is left for clinicians

Statin Intensity

- Moderate Intensity
  - 30-50% reduction in LDL
  - Atorvastatin 10 mg/d
  - Rosuvastatin 10 mg/d
  - Simvastatin 20-40 mg/d
- High Intensity
  - ≥ 50% reduction in LDL
  - Atorvastatin 80 mg/d
  - Rosuvastatin 20 mg/d

Risk Assessment

- 10-yr risk estimate for an ASCVD event Vs. CHD risk with Framingham score
- ASCVD event: nonfatal MI, CHD death, fatal or nonfatal stroke
- New Pooled Cohort Risk Assessment Equations
- Use provided calculator to calculate risk for primary prevention purposes

Hypertriglyceridemia

- Normal is < 150 mg/dL
- Increased risk for pancreatitis with TG > 500 mg/dL, especially if > 1000 mg/dL
- Treatment is indicated to lower risk for pancreatitis by lowering TG < 500 mg/dL, then focus should be turned to LDL reduction
- Fibrates are best agents for lowering TG

Pharmacotherapy: Statins

- HMG-CoA Reductase Inhibitors
- Most potent LDL and TC lowering agents
- Reduce risk for CHD, stroke, and death
- "Rule of 6"
- "Pleiotropic effects"

	LDL Lowering (%)	Dosing Range (mg)	Metabolism
Atorvastatin	26 to 60	10-80	CYP 3A4
Simvastatin	26 to 47	5-40*	CYP 3A4
Rosuvastatin	45 to 63	5-40	CYP 2C9/2C19

*Dose of 80 mg should be avoided 2/2 myopathy/rhabdomyolysis unless tolerating > 12mo

Pharmacotherapy: Statins

- Labs:
  - Baseline LFTs, baseline CK in high risk pts
  - During therapy, LFTs or CK may be checked if suspicion for liver disease or myopathy
- Safety
  - If LFTs > 3x ULN, reduction of dose or D/C is rec'd
  - If severe unexplained muscle symptoms develop, D/C statin and investigate rhabdomyolysis
  - If mild-to-moderate muscle symptoms develop, D/C statin until symptoms resolve, re-introduce at lower dose
  - Statins are C/I in pregnancy (Category X)

Pharmacotherapy: Statins

- Rhabdomyolysis
  - Breakdown of muscles and spilling of their contents into bloodstream
  - Elevated Cr and CK. Brown (tea-colored) urine
  - Complications include ARF 2/2 myoglobin forming tubular casts, hyperkalemia and arrhythmias, compartment syndrome, death
  - High risk if on statin and fibrates (esp gemfibrozil) or any agent that inhibits statin metabolism (cyclosporine, erythromycin, verapamil, amiodarone..)

Pharmacotherapy: Niacin

- Nicotinic acid (Vitamin B_3) at high doses
- Primarily increases HDL by 15-35%, but also reduces LDL and TG
- Shown to reduce CHD events and mortality when combined with a statin
- ER formulation (Niaspan) is preferred to minimize AEs
- Usual dose (ER): 500-2000 mg HS- start low and go slow

Pharmacotherapy: Niacin

- Labs: uric acid, BS/A1c, and LFTs at baseline. Regular monitoring during titration, then every 6 mo once on a stable dose
- AEs: flushing and hepatotoxicity associated mainly with non-ER formulations, may increase uric acid or glucose
- Caution in pts with gout or DM
- Can take NSAID/ASA prior to Niaspan to minimize flushing

Pharmacotherapy: Fibrates

- Fenofibrate, gemfibrozil
- Primarily used to decrease TG by 20-50%, but also increase HDL by up to 30%
- Clinically fibrates are used to lower TG < 500 mg/dL for pancreatitis prevention, after which LDL-lowering therapy should be the target
- AEs: GI symptoms, myopathy and rhabdomyolysis, rare hepatotoxicity, gallstones

Pharmacotherapy: Fibrates

- Labs: obtain CK/LFTs at baseline, recheck periodically or when suspicion arises
- Adding gemfibrozil to a statin should be avoided
- In pts with high TG (> 400 mg/dL), gemfibrozil may increase LDL by 10-30%

Pharmacotherapy: Bile Acid Sequestrants

- Cholestyramine, colesevelam, colestipol
- Bind bile acid and form a complex that gets excreted in feces, which forces liver to use up cholesterol stores
- LDL lowering: 15-30 %
- Used as adjunct with statins- avoid using alone
- AEs: constipation, flatulence, and bloating reported in about 20%

Pharmacotherapy: Bile Acid Sequestrants

- Initiate at low dose, titrate slowly to increase tolerance 2/2 high rate of non-compliance
- Can inhibit absorption of ADEK vitamins and some drugs, should be separated by several hours
- May increase TG levels → should not be used if TG ≥ 300 mg/dL

Pharmacotherapy: Ezetimibe

- Cholesterol absorption inhibitor that leads to compensatory up-regulation of LDL receptors
- Reduces LDL by average of 18%
- Used as adjunct to statins or in statin-intolerant pts
- Fairly safe to use

Pharmacotherapy: Omega-3 Fatty Acids

- Predominant fatty acids in fish oil
- Can lower TG by 35%, but also TC, LDL, and raise HDL
- Reduce platelet aggregation- caution if bleeding risk
- FDA approved dose: 4 g QD for hyper-TG
- Non-prescription grade can be contaminated with mercury and organic pollutants
- Well-tolerated, minimal AEs

Therapeutic Monitoring

- Most agents will reach their max effect by 4-6 weeks of initiation or dose change
- A fasting lipid panel should be checked within 4-12 wks of initiation or dose adjustment, and every 3-12 months thereafter
- Combining non-statins with statins has not been shown to reduce ASCVD events and is not recommended
- Non-statins may only be considered as combination or alternative if pts are intolerant of statins or inadequately responsive to them